REMARKS

Amendments to the Claims

Claims 1-3 and 45-52 are pending. The Applicants respectfully ask the Examiner to replace all prior versions and listings of claims in the present application with the listing of claims currently provided. Claims 1, 3, and 45-51 were amended; Claims 2, 3 and 52 were canceled; and Claims 53-60 are new. The Applicants hereby state that the amendments to the claims do not add new subject matter to the specification.

Amendment support for "one or more" of the various biological persistence enhancing components recited in Claims 1, 45, 47, 49, 51, 54, 56, 58, 59 and 60 can be found at, *e.g.*, ¶¶ 141; 157; 219; 284; 288.

Amendment support for locating a biological persistence enhancing component within the "N-terminal 30 amino acids of the light chain" or the "C-terminal 50 amino acids of the light chain" recited in Claims 1, 45, 47, 49, 51, 54, 56, 58, 59 and 60 can be found at, *e.g.*, ¶ 283.

Amendment support for a biological persistence enhancing component increasing the "half-life" of the modified botulinum neurotoxin type A recited in Claims 1, 45, 47, 49, 51, 54, 56, 58, 59 and 60 can be found at, *e.g.*, ¶ 19.

Amendment support for the recited SEQ ID NOs recited in Claims 45, 47, 49, 54, 56, 58, and 59 can be found at, *e.g.*, ¶ 113; and the Sequence Listing.

Amendment support for the recited SEQ ID NOs recited in Claims 46, 48, 50, 55, and 60 can be found at, *e.g.*, Table 1; and the Sequence Listing.

Amendment support for the recited SEQ ID NO recited in Claim 51 can be found at, *e.g.*, ¶ 140; and the Sequence Listing.

Amendment support for Claim 53 can be found at, *e.g.*, ¶ 112.

Notice to Comply Pursuant to 37 C.F.R. §§ 1.821-1.825

The Examiner has objected to the Sequence Listing under 37 C.F.R. §§ 1.821-1.825, because each sequence disclosed did not allegedly appear in the Sequence Listing and in the text of the description and claims whenever described.

The Applicant has submitted an amended copy of the computer readable form (CRF) of the Sequence Listing and the written Sequence Listing. The Sequence Listing information recorded in CRF is identical to the written Sequence Listing. The Sequence Listing provided does not contain any new matter as required by 37 C.F.R. §§ 1.821(e), 1.821(f), 1.821(g) and 1.825 (b).

Please not that the Applicants request further clarification regarding the Examiner's comments that "page 13 line 26 was not addressed for the four amino acid sequence, in which SEQ ID NOs: 14 & 15 end with NYKD and MYKD." See, August 9, 2007 Office Action at p. 2, ¶ 1, lines 3-5. The May 24, 2007 Applicants Reply amended ¶ 51 (the Applicants are inferring that this is what the Examiner is referring to by "page 13 line 26") to provide SEQ ID NOs for all amino acid sequences of four residues or longer. See May 24, 2007 Applicants Reply at p. 3, number 4. The Applicant's tried calling the Examiner for clarification, however his voicemail indicated that he would be out of the office until November 13, 2007. As such, the Applicants request further clarification of the Examiner's objection because the Applicants do not know what is required of them.

Information Disclosure Statement under 37 C.F.R. 1.98(a)(2)

The Examiner has objected to the information disclosure statement (IDS) filed on May 5, 2005 for non-compliance pursuant to 37 C.F.R. 1.98(a)(2) for failing to provide a legible copy of the listed references.

The Applicants have resubmitted a revised PTO-1449.

Rejections Pursuant to 35 U.S.C. § 112, ¶ 1 Written Description

The Examiner has rejected Claims 1-3 and 45-52 as allegedly lacking written description support under 35 U.S.C. § 112, ¶ 1. The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

The Examiner contends that the present specification neither provides "proper antecedent basis nor conception in context" that describes a modified botulinum toxin type A with increased biological persistence "comprising at least one additional amino acid sequence comprising SEQ ID NO: 27." See, August 9, 2007 Office Action at p. 4, ¶ 1, lines 1-5. The Examiner asserts that the specification solely describes a recombinant construct with having SEQ ID NO: 27 deleted from the N-terminus and SEQ ID NO: 28 deleted from the C-terminus that reduces biological persistence. See, August 9, 2007 Office Action at p. 4, ¶ 1, lines 5-12.

SEQ ID NO: 27

The Applicants respectfully submit that the present specification provides written description support for one or more additional amino acid sequences comprising SEQ ID NO: 27 within the N-terminal 30 amino acids of a BoNT/A light chain, as recited in Claim 1.

First, the present specification discloses that the addition of SEQ ID NO: 27 to a toxin increases biological persistence. SEQ ID NO: 27 comprises amino acids 2-9 of the N-terminal region of the BoNT/A light chain. See, *e.g.*, SEQ ID NO: 29. The present specification states that "[i]n some embodiments, the fusion of, addition to, or swapping of the N-terminal region of the light chain of BoNT/A into a chimeric construct results in an increase in biological persistence and/or enzymatic activity." See, Present specification at ¶ 284, lines 1-3. Thus, the present specification clearly describes that the addition of SEQ ID NO: 27 to a toxin results in an increase in biological persistence.

Second, the present specification discloses that one or more additional amino acid sequences comprising SEQ ID NO: 27 can be added to the N-terminal 30 amino acids of a

BoNT/A light chain. For example, the specification indicates that "[a] modified light chain may include a light chain from botulinum toxins A, B, C1, D, E, F or G. One or multiple domains at the N- and/or C-terminus may be modified by addition, deletion or substitution." See, Present specification at ¶ 288, lines 1-3. The present specification illustrates this concept by describing how a modified BoNT/E can be made by "adding or replacing/substituting one or more N- and/or C-terminal end sequences derived from BoNT/A light chain, thereby resulting in a [modified BoNT/E] light chain with one or both terminal ends having one or more sequences which convey an increased or decreased ability to localize to a plasma membrane, increased or decreased biological persistence and/or an increased or decreased enzymatic activity." See, Present specification at ¶ 288, lines 3-10. As such, the present specification clearly describes that one or more biological persistence enhancing components, like SEQ ID NO: 27, can be added to the N- terminus of a light chain in order to increase biological persistence.

Taken together, the present specification provides written description support for the presently claimed toxins of Claim 1. Although the Applicants maintain that the phrase "at least one additional amino acid sequence comprising SEQ ID NO: 27" has adequate written description support, the Applicants have amended Claim 1 to recite "one or more additional amino acid sequences comprising SEQ ID NO: 27," a phrase that has literal support in the present specification. In it the Applicants position that this amendment has not in any way surrendered any subject matter.

Leucine-based motifs

The Applicants respectfully submit that the present specification provides written description support for one or more leucine-based motifs within the C-terminal 50 amino acids of a BoNT/A light chain, as recited in the present Claim Set.

First, the present specification discloses that a leucine-based motif is a biological persistence enhancing component. See, *e.g.*, ¶¶ 39; 53; 55; 109; 125; 218; and 219. Thus, the present specification clearly describes that the addition of a leucine-based motif to a toxin results in an increase in biological persistence.

Second, the present specification states that a modified BoNT/A can be modified "by adding one or more leucine based motifs, or other structure(s) which contributes to localization of the type A light chain to the plasma membrane, thereby resulting in a light chain with an increased ability to localize to a plasma membrane. This may result in an increase in the biological activity and/or biological persistence of the light chain A. The biological persistence and/or activity of the modified light chain may be about 1.5 to about 5 times that of an unmodified type A light chain." Present specification at ¶ 157. Furthermore, as discussed above, the present specification discloses that one or more leucine based motifs can be added to the C-terminal 50 amino acids of a BoNT/A light chain. See, Present specification at ¶ 288.

Taken together, the present specification clearly describes that leucine-based motifs can be added to the C-terminal 50 amino acids of a BoNT/A light chain in order to increase biological persistence. Although the Applicants maintain that the phrase "at least one additional leucine-based motif" has adequate written description support, the Applicants have amended the claims to recite "one or more additional leucine-based motifs," a phrase that has literal support in the present specification. In it the Applicants position that this amendment has not in any way surrendered any subject matter.

Tyrosine-based motifs

The Applicants respectfully submit that the present specification provides written description support for one or more tyrosine-based motifs within the C-terminal 50 amino acids of a BoNT/A light chain, as recited in Claim 51.

First, the present specification discloses that a tyrosine-based motif is a biological persistence enhancing component. See, *e.g.*, ¶¶ 53; 55; 125; 218; and 219. The present specification also states that "[t]yrosine-based motifs can act in a manner that is similar to that of leucine-based motifs." See, Present specification at ¶ 140, lines 4-5. Thus, the present specification clearly describes that the addition of a tyrosine-based motif to a toxin results in an increase in biological persistence.

Second, as discussed above, the present specification discloses that one or more leucine based motifs can be added to the C-terminal 50 amino acids of a BoNT/A light chain. See, Present specification at ¶ 288. In addition, Example 4 describes administering a "modified neurotoxin compris[ing] a leucine-based motif and/or additional tyrosine-based motifs." See, Present specification at ¶ 193. Similarly, Example 6 indicates that a patient can be treated with a modified neurotoxin that "is botulinum type A, B, C1, C2, D, E, F or G comprising additional tyrosine-based motifs." See, Present specification at ¶ 198.

Taken together, the present specification clearly describes that tyrosine-based motifs can be added to the C-terminal 50 amino acids of a BoNT/A light chain in order to increase biological persistence. Although the Applicants maintain that the phrase "at least one additional tyrosine-based motif" has adequate written description support, the Applicants have amended the claims to recite "one or more additional tyrosine-based motifs," a phrase that has literal support in the present specification. In it the Applicants position that this amendment has not in any way surrendered any subject matter.

Any amino acid

Currently amended Claim 45 does not recite the phrase "at least one amino-acid" that is any "acidic amino acid."

Conclusion

For the reasons discussed above, the Applicants respectfully submit that the presently amended claims are supported by the disclosure of the present specification. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 112, ¶ 1 written description rejection against Claims 1-3 and 45-52.

Rejections Pursuant to 35 U.S.C. § 112, ¶ 1 Enablement

The Examiner has rejected Claims 1-3 and 45-52 as allegedly lacking enablement under 35 U.S.C. § 112, ¶ 1. Specifically, the Examiner contends that the present specification does not reasonably provide enablement as to what minimal structural requirements are necessary for the claimed modified BoNT/A molecules. See, August 9, 2007 Office Action at p. 7, ¶ 1, lines 3-9. The Examiner has suggested that claims directed toward a modified BoNT/A with increases half-life and structurally defined tyrosine-based motifs and leucine-based motifs may obviate this rejection. The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

The Applicants respectfully submit that presently amended Claims 1-3 and 45-52 are directed toward a modified BoNT/A with increased half-life and structurally defined tyrosine-based motifs and leucine-based motifs. Thus, the Applicants respectfully request withdrawal of the 35 U.S.C. § 112, ¶ 1 enablement rejection against Claims 1-3 and 45-52.

Rejections Pursuant to 35 U.S.C. § 112, ¶ 2 Indefinite

The Examiner has rejected Claims 1, 3 and 45-52 as allegedly being indefinite under 35 U.S.C. § 112, ¶ 2. The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

The Applicants respectfully submit that presently amended Claims 1, 3 and 45-52 are definite and respectfully request withdrawal of the 35 U.S.C. § 112, ¶ 2 indefinite rejection against Claims 1, 3 and 45-52.

CONCLUSION

For the above reasons the Applicants respectfully submit that the claims are in condition for allowance, and the Applicants respectfully urge the Examiner to issue a Notice to that effect. Should there be any questions, the Examiner is invited to call the undersigned agent.

Please use Deposit Account 01-0885 for the payment of any extension of time fees under 37 C.F.R. § 1.136 or any other fees due in connection with the current response.

Respectfully submitted,

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